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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,679	04/11/2001	RACHEL BAR-SHAVIT	108366	3009

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,679	BAR-SHAVIT, RACHEL	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,9,10,20,21,23,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,9,10,20,21,23,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the application

The indicated allowability of claims 1, 5, 9, 10, 20, 21, 23, 27 and 28 is withdrawn in view of the following new rejections.

Specification

The use of the trademark MATRIGEL has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 23 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims are directed to an antisense molecule that is an expression vector and are indefinite because the term antisense molecule is recognized by the skilled artisan as a nucleic acid that hybridizes

to a target gene sequence. While an expression vector might comprise an antisense molecule, an expression vector is not itself an antisense molecule.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 9, 10, 20, 21, 23, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting invasiveness of metastatic tumor cells *in vitro*, does not reasonably provide enablement for a method of inhibiting invasiveness of metastatic tumor cells in any organism, a method of inhibiting invasiveness of placental cytotrophoblast cells, or pharmaceutical compositions comprising SEQ ID NO: 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claimed invention is directed to methods of inhibiting invasiveness of metastatic tumor and methods of inhibiting invasiveness of placental cytotrophoblast cells using an antisense molecule or expression vector comprising the sequence defined as SEQ ID NO: 7 that hybridizes to an RNA sequence of a thrombin receptor.

Claims 10 and 23 are directed to pharmaceutical compositions comprising an antisense molecule or expression vector comprising the sequence defined as SEQ ID NO: 7. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism. The instant specification does not enable use of a composition as a therapeutic in an organism as described more fully below. The rejection with regard to claims 10 and 23 may be overcome by removing the word "pharmaceutical" from the preamble of these claims.

The specification provides examples wherein a vector expressing an antisense cDNA of thrombin receptor reduced invasiveness of a metastatic breast cancer cell line in an *in vitro* MATRIGEL assay. Assays using the basement membrane solution MATRIGEL are recognized by the art as a model for measuring the degree of invasiveness of any type of cell. The prior art suggests that thrombin is involved in tumor cell invasiveness and metastasis, and the specification further describes that there is a temporal pattern of thrombin receptor mRNA expression in placental biopsies. The specification does not provide any examples wherein an antisense targeted to thrombin receptor is used to modulate the expression of thrombin receptor in placental

tissue and provides no working examples wherein any antisense molecule or vector was administered to any type of cells in any organism *in vivo*.

Claims 1, 5 and 27 are directed to methods of using a nucleotide sequence that comprises SEQ ID NO: 7 to inhibit invasiveness of metastatic tumor cells. SEQ ID NO: 7 is claimed as hybridizing to an RNA sequence of a thrombin receptor. Claims 9, 10 and 20 are directed to an antisense molecule that comprises SEQ ID NO: 7. The specification illustrates the sequence of the thrombin receptor, SEQ ID NO: 5, in figure 1 and SEQ ID NO: 7 in figure 2. A comparison of these figures shows that SEQ ID NO: 7 is not an antisense molecule that hybridizes to a thrombin receptor but is in fact identical to a portion of the sequence of figure 1. While the specification describes the use of an expression vector encoding an antisense to inhibit thrombin receptor expression, the specification provides no examples where a fragment of thrombin receptor inhibits gene expression via sense inhibition.

The scope of claim 1 encompasses the use of SEQ ID NO: 7 to hybridize to an RNA sequence of a thrombin receptor. The use of the phrase "an RNA molecule" encompasses fragments of the RNA sequences of thrombin receptors, including fragments that show no homology or complementarity with SEQ ID NO: 7. The specification describes the use of SEQ ID NO: 7 to inhibit expression of a full-length mRNA of thrombin receptor, but the specification does not teach how to use this sequence to hybridize to fragments of thrombin receptor RNA that do not comprise SEQ ID NO: 7 or its complement.

In addition to the issues described above, the specification does not provide an enabling disclosure for use of any antisense oligonucleotide *in vivo* in any organism. Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of invasiveness of tumor cells or placental cytotrophoblast cells, as claimed. The specification provides examples wherein nucleic acids are administered to cells in culture, however, the methods of delivery to the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these

teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art do not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

In addition to the general unpredictability of delivery of nucleic acids to an organism, methods of administering nucleic acids to placental cells have additional challenges. See for example Audus (European Journal of Pharmaceutical Sciences 1999), who teaches that researchers have come to realize that placental cells have the ability to actively control transport of molecules. Audus teaches at page 162 that in order to readily permeate the placental barrier, molecules must be relatively lipophilic, have a low degree of ionization and have molecular weights of less than about 600 Da and at page 163 that placental cells express a number of carrier mechanisms such as amino acid transporters that are of unknown physiological significance. Given the teachings of Audus, one of skill in the art would recognize delivery of nucleic acids to

placental cells to be unpredictable due to the nature of the placental barrier and that this unpredictability exists in addition to the generalized difficulties encountered in administering a nucleic acid to an organism and having it enter the targeted cell and remain in sufficient concentration for sufficient amount of time to have a measurable effect.

Even if nucleic acids targeted to thrombin receptor could be delivered across the placental barrier, it is unclear if this would prevent the invasiveness of placental cytotrophoblast cells. The specification indicates that thrombin receptor expression in placental tissue is temporal and provides a vague indication of when expression is increased or decreased in placental tissue which has been displaced from implantation, it is unclear whether antisense would change thrombin receptor levels to a degree to have a measurable effect on the invasiveness of cytotrophoblast cells.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of inhibiting the invasiveness of either metastatic tumor cells or placental cytotrophoblasts cells in any organism using an antisense targeted to thrombin receptor as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1, 5, 10, 21, 23, 27 and 28 are not enabled.

Response to arguments: enablement

In the remarks filed 3/1/05 responding to the previously applied enablement rejection, applicant asserts that the *in vivo* experiments described in the Declaration filed June 17, 2004, clearly overcome any general teaching that it can be difficult to deliver antisense molecules. Applicant further asserts that the amendment to claim 1 to recite that the tumor cells are of epithelial origin and the amendment to claim 27 to recite a method of inhibiting invasiveness of placental cytotrophoblast cells recite methods that are clearly enabled by the specification. These arguments are not persuasive because the experiments described in the declaration describe administration of an antisense vector to *in vitro* cells that are subsequently grafted onto a mouse. This does not provide an example of *in vivo* administration of a nucleic acid and thus does not address the art-recognized issues of delivery described by Opalinska et al. Neither the specification nor the declaration provide specific guidance that would allow the skilled artisan to overcome the art-recognized unpredictability of nucleic acid delivery as set forth in the rejection.

Applicant also argues that the references accompanying the declaration of June 17, 2004 demonstrate there was significant guidance in the art as to how to make and use antisense oligonucleotides. While the examiner agrees that making antisense oligonucleotides and their use *in vitro* was routine in the art at the time of filing, the state of the art does not recognize *in vivo* use as predictable. Of the references cited, only three describe actual *in vivo* administration of nucleic acids and two of these, Panegyres et al. and Sibille et al., involve specialized administration to the site of action of the

oligonucleotides. These teachings found in these three references are not sufficient to demonstrate the delivery of antisense oligonucleotides *in vivo* is generally predictable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 9, 10 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Coughlin (US 6,197,541).

Claims 9, 10 and 20 are directed to compounds and compositions of an antisense molecule comprising SEQ ID NO: 7 and a vector encoding this sequence.

Coughlin discloses in example 1 the isolation of a recombinant thrombin receptor, illustrated in figure 1 and designated as SEQ ID NO: 219. The sequence was isolated from an mRNA library that, when injected into Xenopus oocytes, contained this sequence in HEPES, a pharmaceutically acceptable carrier. Nucleotides 64-611 of SEQ ID NO: 219 comprise the entirety of SEQ ID NO: 7. The alignment of SEQ ID NO: 219 and SEQ ID NO: 7 can be accessed through PAIR on page 42 of the search notes (document code is SRNT) dated 12/23/2003. Coughlin disclose at column 14 that this DNA can be produced by expression from a vector.

Thus, Coughlin discloses all limitations of and anticipates claims 9, 10 and 20.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 2, 2006

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